PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	24.05.2004
Applicant's or agent's file reference: 335-148PCT	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA 03/01229	19.08.2003	19.08.2002

International Patent Classification (IPC) or both national classification and IPC
A01N43/50

Applicant
LORUS THERAPEUTICS INC. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 19.12.2004

Name and mailing address of the international preliminary examining authority:
European Patent Office
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Authorized Officer
Klaver, J

Formalities officer (incl. extension of time limits)
Hutterer, G

I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-72 as originally filed

Claims, Numbers

1-20 as originally filed

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-8,10-14,16-18: No
Inventive step (IS)	Claims	7 (insofar as novel),9,15: No
Industrial applicability (IA)	Claims	3,10,11,16-20: Yes

2. Citations and explanations

see separate sheet

1). Document WO 03/004023 A1 (= D3) was published on 16.01.03 which is after the priority date of 19.08.02 as claimed by the present application.
Provided that this priority has been validly claimed, D3 does not form part of the prior art (Rule 64.1 (b) (ii) PCT).
However, in the European phase of the application D3, claiming an earlier priority of 06.07.01, will be relevant prior art pursuant to Art. 54 (3) EPC.
D3 discloses benzimidazole compounds within the scope of present formulae (I), exemplifying 2-(3-indolyl-)benzimidazole compounds within the scope of formula II (D3: examples 45 and 64) and the use of such compounds for the treatment of diseases associated with microgiglia activation which include inflammatory diseases associated with bacterial infections (D3: page 21, line 16 - 19). D3 further discloses (pharmaceutical) compositions comprising these compounds (D3: page 23, line 20 ff.).
D3 thus anticipates the novelty (Art. 54 (3) EPC) of present claims 4, 6, 8, 10 and 17.

2). Claims 1 - 8, 10 - 14 and 16 - 18 are not novel (Art. 33 (2) PCT for the following reasons:
WO 00/78761 A1 (= D1) discloses 2-(3-indolyl)-benzimidazoles within the scope of Formulae (I) and (II) and their use as antimicrobial or antiinfective agents, in particular against antibiotics resistant bacteria, thus anticipating the novelty of present claims 1 - 6, 8, 10 - 14, 16 and 17.

EP 77 024 A2 (= D2) discloses 2-heteroaryl-4,5-diphenyl-imidazoles and their use as anti-inflammatory agent e.g. against inflammations associated with bacterial (e.g. Mycobacterium) infections (D2: page 3, paragraphs 3 - 7). D2 further discloses pharmaceutical preparations comprising such compounds (D2: page 6, paragraphs 3 and 4). An exemplified compound (4,5-bis-(4-methoxyphenyl)-2-(3-indolyl)-imidazole: D2: example 17) is within the scope of present claim 18.
D2 thus anticipates the novelty of claims 4 - 6, 8, 10, 11, 16 and 18.

WO 02/46168 A1 (= D4) discloses 2-(aryl/heteroaryl)-benzimidazoles and their use as estrogen receptor ligands, including a 2-(3-indolyl)-substituted derivative within the scope of present claim 17 (D4: example 44). D4 further discloses the preparation of pharmaceutical formulations comprising such compounds (D4: page 14, line 6 - 23)
D4 thus anticipates the novelty of present claims 10, 16 and 17.

Further compounds/compositions within the scope of present claims 10, 16, 17 and/or 18

have been disclosed in US 4,721,670 (= D5: compound (10) in col. 5, which is not disclaimed by present claim 18; specific compounds (2) - (9) and the generically disclosed compounds (col. 2, line 34 - col. 3, line 29) are within the scope of present claim 17), WO 98/27065 A1 (= D6: Table 3 (entry 74) and claim 145) and JP 11 199 582 A (= D7: Formula I and compound 2 in Table 1).
Isikdag et al., 1995 (= D8) disclose nematicidal compositions comprising 2,3,5-triphenyl substituted imidazoles thus anticipating the novelty of present claims 10 and 16.

The following document has not been cited in the International Search Report but is considered relevant prior art, at least for the compositions as defined by present claim 16 and their use as defined by present claims 4 - 7, 10 and 11: **WO 93/14081 A1** (= D10).
D10 discloses triaryl/heteroaryl substituted imidazoles within the scope of present Formula (I) (see: D10, page 2, frpom line 5 onwards) and medicaments comprising these compounds for the treatment of diseases exacerbated or caused by excessive or unregulated cytokine production. The substituted imidazole compounds are in particular capable of inhibiting proinflammatory cytokines such as IL-1, IL-8 or TNF which are also implicated in mediating diseases such as sepsis or septic shock (see D10: page 21, line 21 - page 22, line 35). The imidazole compounds of D10 further are considered useful in the treatment of viral infections (D10: page 22, line 36 - page 23, line 18).
D10 thus anticipates the novelty of claims 4 - 7, insofar as these claims define the use of a compound of Formula (I) in the treatment of a disease or disorder **associated with a microbial or fungal infection**, 10, 11 and 16.

A copy of D10 is sent with this Written Opinion.

3). Claims 7, 9 and 15 are not considered to be based on an inventive step (Art. 33 (3) PCT) for the following reason:
The subject-matter of claims 7, 9 and 15 differs from the closest prior art (= D1) in the use of the tri-aryl-substituted imidazoles (including 2-aryl substituted benzimidazoles) of Formula (I) against a fungal infection instead of against a bacterial infection. It appears from the only example illustrating this use (example 32, Table 6) that many compounds within the scope of Formula (I) are not effective in such an antifungal use. It thus appears, that the problem underlying said claims 7, 9 and 15 has not been solved over the whole scope claimed.

4). Compounds as defined by claims 19 and 20 have not been disclosed in the prior art.

said claims hence are novel. It can be seen from Table 3 that these compounds have an advantageous antibacterial effect against various Staphylococcus strains, including methicillin resistant strains. Such an effect has not been disclosed or suggested in the prior art. Said compounds hence are considered an inventive contribution to the prior art (Art. 33 (2) and (3) PCT).

5). Claim 18 defines compounds of Formula (III) excluding various specific compounds, some of which are known from D5. These disclaimed compounds, however, are still within the scope of claim 17 defining compounds of Formula (II), which encompasses Formula (III) of claim 18.
On page 16, line 15/16, it is said that the compound of formula (II) is "other than 3,3'-[5-(4-methoxyphenyl)-1H-imidazole-2,4-diyl]bis-1H-indole" suggesting that this compound is not part of the invention. This compound, however, is not disclaimed from claims 17 or 18.
Claims 17 and 18 hence are neither consistent with one another nor with the description rendering the intended scope of protection ambiguous, contrary to the requirements of Art. 6 PCT.

6). Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D2 and D5 is not mentioned in the description, nor are these document/s identified therein.
It further appears, that there is no background art cited which is relevant for the provisos of claim 18. Applicant is requested to indicate which further prior art than D5 is relevant for these provisos (Rule 5.1 (a) (ii) PCT)..

7). For the assessment of the present claims 1, 2, 4 - 9 and 12 - 15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.